

Pursuant to the telephonic restriction requirement made by the Examiner, applicants confirm their election of claims 1-30 drawn to compounds, method of use and compositions. Applicants do not traverse this restriction, but do retain the right to file a divisional or CIP application directed to non-elected claim 31, the process claim.

Claim 26 was rejected under 35 U.S.C. 112, second paragraph, for incompleteness in that the utility of the composition was not recited. Applicants urge that the utility of the composition is in fact recited, since it is described as "an antihypertensive pharmaceutical composition". Applicants note, however, that the claim may be considered indefinite for failing to recite the contemplated dose, and so amend the claim to include the word "antihypertensive" before the words "effective amount" in order to adequately describe the amount of compound to be administered. Applicants urge that amended claim 26 complies with the requirements of 35 U.S.C. 112.

Claims 1-30 were rejected under 35 U.S.C. 101 for double patenting over parent Serial No. 258,484, filed April 28, 1981. Applicants point out that Serial No. 258,484 is in Interference, but an amendment eliminating penta[b]pyrroles (i.e.  $R^4$  and  $R^5$  of the parent application form group "U" wherein  $x^1$ ,  $x^2$  and W are methylene, p is 0 and q is 1) from the scope of the parent application has been submitted in the parent case. A copy of the requested amendment to claim 1 in the parent application is attached for reference (Appendix A). Applicants urge that the rejection under 35 U.S.C. 101 be withdrawn.

Claims 1-30 are rejected under 35 U.S.C. 103 as being obvious over Hoefle et al U.S. Patent 4,344,949 ('949) and U.S. patent 4,404,206 (Vincent et al). Hoefle et al '949 is said to

indicate that the octahydroindole aminoacyl "derivative" would have antihypertensive activity, while Vincent et al is said to show that the penta[b]pyrrole ring system substituted by sulfur is expected to have antihypertensive activity, and that the ring systems are equivalent.

Applicants urge that Vincent et al do not teach or suggest the instant penta[b]pyrrole ring system. Vincent et al describe the "A" ring in very broad terms, but that extreme breadth (i.e., A is mono or bicyclic, saturated or unsaturated, may include heteroatom(s) and may be substituted) makes it all the more unlikely to single out a penta[b]pyrrole ring: there is no reason to choose a penta[b]pyrrole ring based on the disclosure of a virtually unlimited number of compounds, particularly when only 5 ring systems are specifically disclosed and only 2 are claimed.

The fact that Vincent et al discloses a wide variety of ring systems does not establish the equivalence of all the possible ring systems, particularly when so few are specifically disclosed and even fewer are claimed. A Markush group such as "A" in Vincent et al indicates that the claimed compounds as a whole may have equivalent activity, but one skilled in the art must not necessarily conclude that the individual members of the various substituent groups are either chemically or pharmacologically equivalent, with respect to the compound under consideration or in an abstract sense. Since only one perhydroindole (i.e. octahydroindole) is specifically disclosed and no penta[b]pyrroles are disclosed, applicants urge that Vincent et al cannot be said to establish the equivalence of the two ring systems.

The Vincent et al compounds, moreover, differ from the instant compounds in the groups present at the opposite end of the molecule from the fused rings: the reference compounds may contain a variety of simple, unsubstituted radicals in place of the alanyl-nitrogen of the instant invention, while the alanyl-nitrogen of the instant compounds always is connected to an "R-CO-CHR<sup>1</sup>-" group, wherein R and R<sup>1</sup> represent a variety of groups. Applicants urge that the Vincent et al reference, taken alone, does not teach or suggest the penta[b]pyrrole ring system or its equivalence to octahydroindole rings, but that even if it did, there is still no teaching or suggestion that compounds disclosed by Vincent et al and containing those ring systems would be equivalent to penta[b]pyrrole rings attached to the aminoacyl side chains disclosed by applicants.

Hoefle et al '949 is cited to show that octahydroindoles aminoacyl derivatives have antihypertensive activity. Applicants note that octahydroindoles are not "derivatives" of penta[b]pyrroles, but are independently prepared compounds. More importantly, applicants urge that the '949 patent is irrelevant since it is in fact directed to 1,2,3,4-tetrahydroisoquinoline compounds, not to octahydroindoles (i.e., two fused 6-membered rings wherein one ring is unsaturated versus a saturated 6-membered ring fused to an saturated 5-membered ring). A more appropriate reference disclosing octahydroindole aminoacyl compounds is Hoefle et al U.S. patent 4,425,355 ('355). Applicants believe that the '355 patent, however, is equally inapplicable. While Vincent et al is so broad as to be useless in teaching penta[b]pyrroles, Hoefle et al '355 and '949 are so narrow as to be similarly ineffective. Each Hoefle patent discloses one specific ring system and limited substitution

(compared to the instant compounds) for the variables included on the aminoacyl portion, and therefore does nothing to teach or suggest the instant compounds.

To say that the combination of Vincent et al and Hoefle et al renders applicant's compounds obvious is similar to the reasoning rejected in Ex parte Garvey, 41 USPQ 583, wherein it was held that there can be no anticipation where the reference is so broad that the likelihood of arriving at the claimed composition could be "about the same as discovering the combination of a safe from a mere inspection of the dials thereof". See also, In re Petering, 133 USPQ 275 wherein it was held that a broad generic formula does not anticipate all compounds embraced by it merely because they are within the scope of the formula. Where In re Ruschig, 154 USPQ 118, applied this reasoning to hold lack of anticipation of a specific compound, Tosan et al v. Siegel et al, 167 USPQ 361, extended it to apply to a sub-genus; that is, a sub-genus is not anticipated merely because it is part of a vast genus. If this theory is true for anticipation (i.e. where a single compound of sub-genus is completely disclosed in a single reference), it is logical that where references must be combined to allegedly render a claimed compound or subgenus obvious under 35 USC 103, a broad generic teaching in one reference combined with a very specific teaching in another is insufficient to establish obviousness.

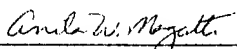
It is well settled that even though references can be combined, that fact does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Bergel, 130 USPQ 206; In re Imperato, 179 USPQ 730. The references must be viewed by themselves and not in retrospect, and must suggest doing what applicants have

done. In re Shaffer, 108 USPQ 326. If at all, it is only by hindsight, after reading applicants' disclosure, that the cited references might be said to render obvious applicants' invention.

It would appear that the allegation of structural obviousness is at least partly based on the Examiner's opinion that with the cited art available, it would be obvious to try to make applicants' claimed compounds. "Obviousness to try", however, is not a valid test of patentability. In re Tomlinson et al, 150 USPQ 623. It is well accepted that one usually undertakes research with the hope of success, and that determinations of patentability based on that criteria would be contrary to statute. In the chemical arts in particular, the fact that it may be obvious to try a new compound will not guarantee that such a compound can in fact be prepared, or that if prepared, it will have the expected or desired activity. It is not the direction of the research that must be unobvious, but rather the compounds produced by that research.

Applicants urge that the cited references, either alone or in combination, do not render obvious the instant genus of aminoacyl-substituted penta[b]pyrroles. Applicants respectfully repeat their request that the rejections be reconsidered and all claims be allowed.

Respectfully submitted,

  
Anita W. Magatti  
Attorney for Applicants  
Reg. No. 29825  
Tel. No. (201) 822-7389